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(71) Applicant (*for all designated States except US*): **GALE-PHAR M/F** [BE/BE]; Rue du Parc Industriel 39, B-6900 Marche-en-Famenne (BE).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **VANDEBIST, Francis** [BE/BE]; Alsebergsesteenweg 1116, B-1650 Beersel (BE). **BAUDIER, Philippe** [FR/BE]; Rue Engeland 338, B-1180 Uccle (BE). **DEBOECK, Arthur** [BE/US]; HCO2 Box 14885, Gurabo, Puerto Rico 00778 (US). **SERENO, Antonio** [BE/BE]; Passiewijk 21, B-1820 Melsbroek (BE).

(74) Agents: **POWIS DE TENBOSSCHE, Roland** et al.; Cabinet Bede, Boulevard General Wahis 15, B-1030 Brussels (BE).

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(54) Title: STABLE CONTROLLED RELEASE PHARMACEUTICAL COMPOSITIONS CONTAINING FENOFIBRATE AND PRAVASTATIN

(57) Abstract: A controlled Release Pharmaceutical composition comprising an effective amount of Pravastatin and Fenofibrate, characterized in that the difference, in absolute value, between the times of maximal concentration (T_{max}) of Pravastatin and Fenofibric acid is not less than 1.5 hours upon administration with food to humans.



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**STABLE CONTROLLED RELEASE PHARMACEUTICAL
COMPOSITIONS CONTAINING FENOFIBRATE AND PRAVASTATIN**

The present invention is aimed at a novel pharmaceutical preparation
5 useful for the treatment of hypercholesterolemia and/or hyperlipidemia.
Disclosed are pharmaceutical dosage forms containing a statin and a
fibrate. In particular, the invention relates to a single unit dose formulation,
containing a mixture of Pravastatin and Fenofibrate.

The invention relates to a stabilised formulation containing Pravastatin. In
10 particular the Pravastatin is stabilised by blending and/or granulating the
Pravastatin with an alkaline substance which imparts a pH of less than 9 to
an aqueous dispersion and/or solution of said composition.

In a preferred composition, the alkaline substance is selected from the
family of carbonates and bicarbonates especially suitable is sodium
15 bicarbonate.

The present invention also discloses a single unit dose formulation which
releases the Pravastatin or its acceptable pharmaceutical salts and the
Fenofibrate at a predefined controlled manner. The formulation is
characterised in vivo in such a manner that the absolute value of the
20 differences between the Fenofibric acid (the active metabolite of
fenofibrate) and Pravastatin time to maximum concentration (T_{max}) after
single dose administration is at least 1.5 hour, advantageously at least 2
hours.

BACKGROUND OF THE INVENTION

Hypercholesterolemia is a main player in the development of atherosclerosis diseases in general and coronary heart diseases in particular. The risk of progression of the atherosclerosis process to coronary heart diseases increases progressively with increasing levels of total serum cholesterol, low density lipoproteins (LDL) cholesterol and triglycerides at both the individual and the population level. Drugs used to treat hypercholesterolemia pertain mainly to the family of statins and fibrates.

The statin family of drugs also called 3-Hydroxy-3Methylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors are reversible inhibitors of the microsomal enzyme HMG-CoA reductase, which converts HMG-CoA to mevalonate which is a precursor in the cholesterol biosynthesis. Inhibition of HMG-CoA reductase by statins decreases intracellular cholesterol biosynthesis, which then leads to transcriptionnally upregulated production of microsomal HMG-CoA reductase at cell surface LDL receptors.

Subsequently, additional cholesterol is provided to the cell by de novo synthesis and by receptor-mediated uptake of LDL-cholesterol from the blood. This resets intracellular cholesterol homeostasis in extrahepatic tissues, but has little effect on the overall cholesterol balance (Clin. Pharmacokinet. 1997, May, 32(5), 403-425).

The most important molecules belonging to the statins family are: pravastatin, simvastatin, atorvastatin, fluvastatin and lovastatin. They differ by their physico-chemical properties and by their pharmacokinetic properties.

Pravastatin sodium produces its lipid-lowering effect in two ways. First, as a consequence of its reversible inhibition of HMG-CoA reductase activity, it effects modest reductions in intracellular pools of cholesterol. This results in

an increase in the number of LDL-receptors on cell surfaces and enhanced receptor-mediated catabolism and clearance of circulating LDL. Second, pravastatin inhibits LDL production by inhibiting hepatic synthesis of very low-density lipoproteins (VLDL), the LDL precursors.

- 5 Pravastatin slows the progression of atherosclerosis in humans and may have beneficial effects in stabilizing plaques, improving endothelial dysfunction, decreasing platelet thrombus formation, improving fibrinolytic activity and reducing incidence of transient myocardial ischaemia.

- 10 Fenofibrate belongs to another class of hypocholesterolemic agents: the fibrates. The lipid-modifying effects of fenofibrate are mediated via the activation of the peroxisome proliferator-activated receptors (PPARs).

- 15 Fenofibrate or p-(4-chlorobenzoyl)-phenoxy isobutyrate isopropyl ester is useful for the treatment of adult patients with very high elevations of serum triglyceride levels and/or cholesterol levels. The usual daily dosage is 100 to 300mg which is administered in one or two doses. Fenofibrate absorbed as fenofibric acid, resulting from the hydrolysis of fenofibrate, is extensively bound to plasma albumin. The plasma half-life is about 20 hours. Fenofibric acid is excreted predominantly in the urine, mainly as the glucuronide conjugate, but also as a reduced form of fenofibric acid and its
20 glucuronides.

- 25 Fenofibrate reduces plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG) and very-low-density lipoprotein (VLDL) cholesterol levels, and increases high-density lipoprotein cholesterol (HDL-C) and apolipoprotein (Apo) AI and Apo AII levels in patients with dyslipidaemia.

Fenofibrate also reduces plasma fibrinogen levels in both normolipidemic individuals and those with dyslipidemia, and is significantly more effective in that reduction than simvastatin, atorvastatin or pravastatin. This is of significance since increased levels of fibrinogen or plasminogen activator

inhibitor (PAI-1) are associated with an increased risk of atherosclerosis and coronary heart disease (CHD).

Fenofibrate has also demonstrated a very important activity in reducing the levels of the inflammatory marker C reactive protein (CRP). The C-reactive
5 protein has been recognized to have a negative effect on the evolution of the pathogenesis of artherosclerosis and coronary heart diseases.

Although each of Pravastatin and Fenofibrate alone have demonstrated their ability to reduce levels of cholesterol in large amount of patients with hypercholesterolemia. There still remains an important number of patients
10 that fail to reach the desired cholesterol levels. Moreover the number of patients failing to reach the desired cholesterol levels dramatically increased when the cholesterol upper limit levels guidance were reduced from 250mg/dL to 200mg/dl. This situation will further worsen since the actual trend is to lower these limits even more to less than 150mg/dl.
15 Patients with increased difficulty to lower their high cholesterol levels include but are not limited to diabetic patients, patients having the metabolic syndrome and patients with mixed severe hyperlipidemia. For all those patients, a combination of a statin with a fibrate would definitely be beneficial in order to normalise their cholesterol levels.

20 While such combination would be very effective in reducing the cholesterol levels, it shall be remembered that the co-administration of a statin and a fibrate is not without potential serious side effects that may lead to patient's death. Therefore it is remembered that the co-administration of the statin cerivastatin (Baycol®) with the fibrate gemfibrozil was responsible for the
25 death of tenth of patients. This situation obliged the USA Food and Drug Administration to interdict the use of such combination. The inventors of the present invention have overcome this problem by controlling the release of the statin (Pravastatin) and the fibrate (Fenofibrate) in such a manner that the maximum blood concentrations of each of the drug does not
30 appear at about the same time after the administration. In particular the

absolute value of the differences between the Fenofibric acid and the Pravastatin plasma levels time to maximum concentration (T_{max}) after single does administration is at least 2 hours.

To increase the safety of the combination product it is essential that the two
5 components (Fibrate and Statin) are taken at very precise predefined times. The invention of the present invention have overcome this problem by combining the two drugs into a single unit dose that contains both drugs with controlled release profile and to be taken once a day.

The therapeutic effect of concomitant administration of fibrates and statins
10 has been evaluated in several clinical studies. For instance, Ellen and al (1998) demonstrated that the combination of fenofibrate combined to either pravastatin 20 mg or simvastatin 20 mg was an effective and safe treatment of combined hyperlipidemia. Feber and al (1995) have assessed the long-term safety of combinations of pravastatin and simvastatin with either
15 bezafibrate or fenofibrate for up to three years and have concluded that the combinations of drugs assessed were not associated with serious disturbances in biochemical markers of liver or muscle function. Shek and Ferill (2001) have reviewed the literature concerning clinical trials performed with fibrate-statins combinations and concluded that this kind of
20 combination therapy offers significant advantages for the treatment of severe or refractory mixed hyperlipidemia. They observed that the risk of myopathy is lower with this kind of combination than with higher doses of statins alone. Farnier and al (2000) have compared the administration of fluvastatin + fenofibrate with fenofibrate in patients with severe primary
25 hypercholesterolemia and conclude that the combination treatment resulted in substantial improvement in atherogenic plasma lipids and is well tolerated. Finally, Athyros and al have assessed the efficacy and safety of a combination of atorvastatin + fenofibrate versus each monotherapy in patients with type 2 diabetes combined with hyperlipidemia. They
30 concluded that the combination was highly beneficial on all lipid parameters

- and improves patient's coronary artery disease risk status significantly more than each drug alone. So it clearly appears that the combination treatment seems interesting to treat some categories of patients with hyperlipidemia. Nevertheless, it should be noted that all studies mentioned hereinabove
- 5 were performed by administering separately the fibrate compound and the statin compounds and therefore failed to provide for a precise control of the pharmacokinetic profile of both drugs and mainly failed to provide for an at least 2 hours differences in the time to maximum (T_{\max}) of each of the statin and the fenofibric acid after single oral dose.
- 10 European Patent Application 455,042 describes a method for treating dyslipidemia by administering a combination of Pravastatin and a fibric acid derivative and European Patent Application 475,148 describes the use of Pravastatin alone or in combination with a fibric acid derivative for the preparation of a pharmaceutical preparation useful in preventing or treating
- 15 Type III hyperlipoproteinemia. Both patents while disclosing the use of Pravastatin and a fibric acid derivatives in combination fail to disclose the need for the difference of time of maximum blood concentration between the 2 active components and also never described is a composition able to deal with the multiple problems linked to fibrate / statin combination.
- 20 A pharmaceutical preparation, to be useful must show acceptable stability properties. This is, to be practical show stability for at least 2 years under the standard ICH regulations. Furthermore, Pravastatin, a 4-hydroxyalkylacid, forms easily upon storage a lactone by losing a molecule of water. The levels of lactone must be kept very low.
- 25 US patent application (20020161032) claims a composition containing fenofibrate and a statin wherein the fed-fasted effects were reduced thanks to the use of a phospholipid as a surface active substance. US patent 6,180,660 describes a method for preventing cardio-vascular diseases using a HMG-CoA reductase inhibitor alone or in combination with another
- 30 lipid altering agents in subjects with specific cholesterol levels.

Nevertheless, these 2 patents fail to disclose how to stabilize pravastatin and to avoid side effects linked to simultaneous high blood levels of both active ingredients.

5 The WO 01/37831 describes a pharmaceutical combination comprising separate dosage form in a common blister card of an inhibitor of the HMG-CoA reductase and a fibric acid derivative useful in the treatment of dyslipidemia of diabetics and non-diabetics. Since this application does not describe a single unit dose, it cannot control the relative apparition of the times of maximum concentration of both drugs.

10 The stability of statins from the family of the 4 hydroxy alkylacid, such as Pravastatin, are a known challenge for the pharmaceutical formulator. Indeed, various environmental factors such as temperature, moisture, low pH, carbon dioxide may cause significant degradation of these compounds.

15 US Patents 5,030,447 and 5,180,589 describe pharmaceutical compositions in the form of a tablet with enhanced stability comprising Pravastatin characterised in that it contains one or more basifying agent to impart a pH of at least 9 to an aqueous solution and/or dispersion of said composition. The use of alkalinising substances who give a pH above 9 is certainly not recommended for the patient stomach and lower pH values, 20 less than 9, which are more physiological are certainly preferred.

US patent 6,531,507 describes a composition containing a statin compound obtained by a process of co-crystallisation and/or co precipitation of the statin compound with a buffering or a basifying substance. This patent describes statin, pure active drug, stabilisation by a process of co- 25 crystallisation and/or co-precipitation that involves solubilising the statin into organic solvent. This process, while very expensive, addresses the stability of the statins presented under the form of pure chemical substances.

Nevertheless, it fails to disclose the stabilisation of a pharmaceutical formulation containing Pravastatin by a process which is cost effective.

Field of the invention

The present invention is aimed at a novel pharmaceutical preparation useful for the treatment of hypercholesterolemia and/or hyperlipidemia.

The combination of a HMG-CoA reductase inhibitor and fenofibrate (administered in two separate dosage forms) is known to be better tolerated and equally if not more efficient as a higher dose of the HMG-CoA reductase inhibitor derivatives in the treatment of hypercholesterolemia because both drugs have complementary and even synergistic mechanism of action as shown in the table hereinbelow

Table : effect of fibrates and statins on the different lipid parameters

Effect	Statin	Fibrate
LDL decrease	+++	+
TG-rich lipoprotein decrease	+	+++
HDL increase	+	++
Postprandial lipemia decrease	±	++
Improvement in LDL size profile	±	++
Prevention of lipoprotein oxidation	++	±
Pleiotropic effects	+++	+
HDL – high density lipoprotein; LDL – low density lipoprotein; TG – triglyceride.		

Some clinicians already prescribe to the same patients separate forms of a statin and of a fibrate. This separate administration has the disadvantage to complicate the posology for the patients, to increase the risk of mistakes or omissions of the drugs intake and does not provide for a precise control of the pharmacokinetics of the active substances which leads to the reduction of the risk of muscular side effects.

Useful formulation should be easy to take, efficacious, reduced side effects and stable. Disclosed are once a day single unit dose formulation containing both Pravastatin and Fenofibrate. The complementary and/or synergistic mechanism of action of Pravastatin and Fenofibrate are known
5 and will render the formulation very attractive to reduce the cholesterol levels in patients in need. The controlled release characteristic of the formulation resulting in the separation in time of the maximum plasma concentration of both drugs will maintain the risk of side-effect of said preparation very low.

10 It is also an object of the present inventions to provide a pharmaceutical composition containing pravastatin and fenofibrate suitable for once daily administration that can be taken in the morning or in the evening. -

The present invention provides also for a stabilised pharmaceutical formulation.

15 It is an object of the present invention to combine in a single dose form a statin, which is pravastatin, and a fibrate, which is fenofibrate. These drugs have the important advantage to possess complementary mechanisms of action. The pharmacological effects of this combination is to act efficiently on the usual lipid triad : LDL, HDL, TG and inflammatory markers like CRP
20 (c-reactive protein).

It is another object of the present invention to provide a pharmaceutical composition comprising a combination of fibrates and statins which is safe. A particular safety concern is the potential for the occurrence of myopathy. Indeed, both kinds of drugs can provoke muscular side effects, leading in
25 the worst case to fatal rhabdomyolysis. Rhabdomyolysis has for instance been observed when cerivastatin was combined to gemfibrozil and resulted in the removal from the market place of Cerivastatin containing drug product.

Also it is an object of the present invention to provide a very efficient hypocholesterolemic treatment to patients in such a need while reducing the risk of side-effects.

It is another object of the present invention to combine into the same
5 pharmaceutical dosage form a statin and a fibrate which are eliminated by
different routes of metabolism. Avoiding the risk of any direct
metabolization interactions between the two drugs of the combination.
Indeed, pravastatin is considered as a particularly safe statin since this
molecule is not metabolised through the cytochrome P450 system, what
10 minimizes the risk of interactions with other drugs or with food. On the
other hand, fenofibrate is not metabolised by cytochrome P450 3A4, the
isoenzyme of the cytochrome P450 system involved in the metabolism
of the majority of drugs and is only weakly metabolised by cytochrome
P450 2C9 isoenzyme (Martindale 2000).

15 Another object of the present invention is the use of pravastatin, a statin
which takes its main activity from the parent drug and not from active
metabolites. Also, the only active metabolite has pharmacokinetic
properties very close to those of the parent drug.

It is another object of the present invention to provide a pharmaceutical
20 composition useful for the treatment of hyperlipidemia comprising
Pravastatin or one of its pharmaceutical acceptable salts and Fenofibrate
characterised that the absolute difference in time to maximum
concentration (T_{max}) of Fenofibric acid and Pravastatin after single dose
administration with food is at least 2 hours.

25 It is an object of the present invention to provide for a pharmaceutical
composition consisting in a capsule containing the Fenofibrate and the
Pravastatin. The capsule can be any type hard or soft gelatin, and/or
Hydroxypropyl Methhylcellulose capsules.

Another object of the present invention is that the Fenofibrate may be present in the pharmaceutical dosage form under the form of micronized powder, micronized Fenofibrate coated onto a carrier and / or beads, co-micronized Fenofibrate with a surfactant such as sodium lauryl sulfate, dispersed and/or dissolved Fenofibrate in polyglycerides, oils, surfactant
5 and mixtures thereof.

The fenofibrate can be formulated as powder to be filled into capsules for instance by micronized active ingredient or co-micronized active ingredient with a surfactant mixed, for instance, with some of the following excipients :
10 pregelatinized starch, lactose, mannitol, magnesium stearate, sacchararose, magnesium stearyl fummarate, silice colloidal or talc.

Fenofibrate can also be dispersed or dissolved in fatty excipients like , but not restricted to polyglycolized glycerides, polyethylene glycols, vegetal or mineral oils, derivatives of fatty acids, medium chain triglycerides. Other
15 non-fatty excipients can be used to improve those formulations like hydroxypropylcellulose, ascorbyl palmitate, antioxydants.

Those suspensions or solutions of fenofibrate in excipients can be filled into hard gelatin or HPMC capsules or used to coat inert beads (for instance sugar or starch) with the said solution or suspension. Fenofibrate can also
20 be granulated with the fatty granules mentioned hereinabove, to obtain either beads or fatty granules of fenofibrate, which can then be compressed or filled into tablets. Fenofibrate beads require the presence in the composition of other excipients allowing the spheronization such as for instance microcrystalline cellulose, lactose, other cellulose derivative,
25 polyvinylpyrrolidone, sucrose stearate.

It is also an object of the present invention to provide Fenofibrate pharmaceutical composition presenting modified release profiles such as: immediate release, delayed release, extended release and any combination thereof.

It is another object of the present invention to provide a stabilised Pravastatin, pharmaceutical composition under the form of Pravastatin sodium salt.

Another aspect of the present invention is to provide the Pravastatin sodium
5 salt under the form of powder, tablet, beads obtained by extrusion
spheronization, beads obtained by coating inert or active support.

Powder of pravastatin can be obtained by direct mixing of the active
ingredient with for example lactose monohydrate, mannitol, sodium
bicarbonate, calcium hydrogenophosphate, silice colloidal, magnesium
10 stearate or magnesium stearyl fumarate. Powder of pravastatin can also
be obtained by granulation of the active ingredient with lactose, sodium
bicarbonate, calcium hydrogenophosphate, mannitol, microcrystalline
cellulose, polyvinylpyrrolidone, sodium croscarmellose, polyplasdone,
sodium starch glycolate, magnesium stearate or magnesium stearyl
15 fumarate. The powder so obtained may be filled into hard gelatin or HPMC
capsules.

Tablets of pravastatin can be obtained by direct compression or wet
granulation. Excipients which can be used but not restricted to for direct
compression : lactose, sodium bicarbonate, calcium hydrogenophosphate,
20 mannitol, polyvinylpyrrolidone, sodium croscarmellose, polyplasdone,
sodium starch glycolate, magnesium stearate or magnesium stearyl
fumarate. Excipients which can be used but not restricted to for wet
granulation are : lactose, sodium bicarbonate, calcium
hydrogenophosphate, mannitol, microcrystalline cellulose, ascorbyl
25 palmitate polyvinylpyrrolidone, sodium croscarmellose, polyplasdone,
sodium starch glycolate, magnesium stearate or magnesium stearyl
fumarate.

Beads of pravastatine obtained by extrusion-spheronisation may content
(but are not restricted to) one or more of the following excipients :

microcrystalline cellulose, lactose, sodium carboxymethylcellulose, sucrose stearate, polyethyleneglycol, ascorbyl palmitate, polyvinylpyrrolidone, hydroxypropylmethyl cellulose or another cellulose derivative.

5 Inert beads may be beads of sugar or starch or other any other pharmaceutically acceptable excipients. those beads can for example be coated with an aqueous solution of pravastatin together with, for example, polyvinylpyrrolidone, hydroxypropylmethylcellulose, polyethyleneglycol, titane oxide, talc, polysorbate (Tween 80).

10 Another object of the present invention is to provide Pravastatin formulation stabilised by mixing, blending and/or granulating the Pravastatin with alkaline bicarbonate with or without other pharmaceutical excipients the resulting formulation when dissolved and/or dispersed in water having a pH equal or lower than 9. Any bicarbonate may be used, the preferred being sodium bicarbonate.

15 In another aspect of the present invention the pravastatin formulation contains an antioxidant for improved stability.

The composition of the present invention can advantageously contain, in addition to pravastatin and fenofibrate and suitable excipients, ingredients allowing to control the homocystein levels of patients such as vitamins
20 among the group of vitamins B, minerals or other nutrients. Folic acid, vitamin B6, vitamin B12 and mixtures thereof (especially folic acid and mixture containing folic acid) seem to be particularly suitable to control the homocystein plasma levels of patients. The composition of the present invention can also advantageously contain, in addition to pravastatin and
25 fenofibrate and suitable excipients two or more of the said vitamins or minerals nutrients. For instance a combination of folic acid, vitamin B6 and/or Vitamin B12, can be added to the composition containing fenofibrate and pravastatin.

Another object of the invention is to provide an easy, cost effective and reliable process for manufacturing the fenofibrate-pravastatin stabilized composition: characterised in that to the capsule containing the Fenofibrate is added a tablet (coated or not) or beads (coated or not) of Pravastatin.

DETAILED DESCRIPTION

The definition of the main pharmacokinetic parameters used in the present invention is given hereinbelow. Those definitions are taken from the "Note for guidance on the investigation of bioavailability and bioequivalence" published by the European Agency for the Evaluation of Medicinal Products (EMA).

C_{\max}	Maximal plasma concentration
C_{\min}	Minimal plasma concentration
t_{\max}	Time passed since administration at which the plasma concentration maximum occurs
AUC_t	Area under the plasma concentration curve from administration to last observed concentration at time t.
$t_{1/2}$	Plasma concentration half-life.

Fenofibrate is rapidly absorbed following oral administration. The extent of absorption varies from 30-50% when taken while fasting, but increases to 60-90% when taken after a meal. There is considerable inter-individual variation. Peak plasma levels of the principal active metabolite, fenofibric acid, following a single oral dose of 300 mg fenofibrate are in the range of 6-9.5 mg/L.

Following absorption, presystemic metabolism is virtually complete with rapid conversion of the drug to fenofibric acid (which is the active metabolite of fenofibrate) and others metabolites by intestinal and plasma esterases.

There is some evidence of a correlation between the plasma concentration of fenofibric acid and its lipid lowering effects, although the extent to which

this is seen may depend on the type of hyperlipidaemia (Raslova et al, 1997).

The mean plasma half-life of fenofibric acid is 19.6 - 26.6 hours in healthy, fasting young adults; this is little altered by diet or by repeat administration.

- 5 Fenofibric acid is eliminated mainly in the urine, as a conjugated derivative (fenofibric acid ester glucuronide, 60-88%). Lesser amounts of fenofibric acid and the benzhydrol and its glucuronide are also found in the urine.

There is no evidence of fenofibric acid accumulation following repeated fenofibrate administrations.

- 10 Pravastatin sodium is administered orally in the active form. In clinical pharmacology studies in man, pravastatin is rapidly absorbed, with peak plasma levels of parent compound attained 1 to 1.5 hours following ingestion. Based on urinary recovery of radiolabeled drug, the average oral absorption of pravastatin is 34% and absolute bioavailability is 17%.
15 (Singhvi et al, 1990; Sasahara et al, 1988)

While the presence of food in the gastrointestinal tract reduces systemic bioavailability, the lipid-lowering effects of the pravastatin are similar whether taken with, or 1 hour prior, to meals. (Pan et al, 1993)

- Systemic bioavailability of pravastatin administered following a bedtime
20 dose was decreased by 60% compared to that following morning administration. Despite this decrease in systemic bioavailability, the efficacy of pravastatin administered once daily in the evening, although not statistically significant, was marginally more effective than that after a morning dose. This finding of lower systemic bioavailability suggests
25 greater hepatic extraction of the drug following the evening dose. (Triscari et al, 1991)

Biotransformation of pravastatin, contrary to other drugs of the same class (simvastatin, atorvastatin) does not involve the cytochrome P450 system.

In contrast to other HMG-CoA reductase inhibitors, which depend on their metabolites for their pharmacological activity, 75% of the inhibitory activity of pravastatin is attributable to the parent drug.

Steady-state AUCs, C_{\max} and C_{\min} plasma concentrations do not show
5 evidence of pravastatin accumulation following once or twice daily administration of pravastatin sodium tablets.

The terminal plasma elimination half-life ($t_{1/2\beta}$) of pravastatin ranges from 1.3 to 2.6 hours in both healthy volunteers and patients with hypercholesterolemia. (Pan et al, 1987; Pan et al, 1990; Sasahara et al,
10 1988)

Corresponding values for its major metabolite are 0.8 to 1.3 hours. (Pan et al, 1990)

The use of Pravastatin has been associated with severe myopathy, including rhabdomyolysis side effects which are directly proportional to the
15 dose administered.

The importance of statin side effects became extremely visible during the year 2001 when in August, Baycol[®] (Cerivastatin) had to be removed from the market place following reports of rhabdomyolysis, including related deaths. Cerivastatin revealed an increasing reporting rate of
20 rhabdomyolysis especially when co-administrated with gemfibrozil (a fibrate)

Nevertheless, to reduce to the maximum the potential risk of side-effects, it would be highly desirable to dispose of a combination product with adequate Controlled Release pharmacokinetic properties i.e. a drug
25 product which present the property of giving, after oral administration to humans, mean respective time to plasma peaks (T_{\max}) of each drug sufficiently separated, in order that the plasma level of the first drug released is already significantly decreased when the mean T_{\max} of the

second drug occurs. The present invention discloses a composition combining pravastatin and fenofibrate in a single dosage unit, which upon intake provides different absorption characteristic for each of the drug.

In a preferred embodiment, the present invention discloses a composition
5 containing Pravastatin and Fenofibrate in a single dosage unit which upon intake provides a rapid T_{max} of pravastatin and a longer T_{max} of fenofibrate in such a way that the mean plasma concentration of pravastatin is significantly decreased when mean T_{max} of fenofibric acid occurs. In this manner, high plasma concentrations of both drugs are never reached
10 simultaneously and the risk of side effects, which is proportional to plasmatic concentration of each drug, is minimised.

On the other hand the T_{max} value for each of the drugs should be as separated as possible and ideally the absolute difference between the T_{max} of fenofibric acid and the T_{max} of pravastatin shall not be less than 1.5
15 hours, preferably not less than 2.0 hours. An example of a desired pharmacokinetic profile is described in figure 1 corresponding to plasma profile of both drugs after oral administration of the combination fenofibrate 160 mg + pravastatin 20 mg.

The obtention of such pharmacokinetic profiles is very challenging since the
20 bioavailability of fenofibrate (and hence fenofibric acid) is significantly affected by the intake of food while the bioavailability of pravastatin is almost unaffected. Consequently, to present an adequate pharmacokinetic profile, the combination drug should be taken preferably with food. Unfortunately, the usual effect of food intake on the pharmacokinetic profile
25 of drugs is to delay the T_{max} and also to delay the T_{max} of pravastatin, making the reaching of the goals still more difficult. Surprisingly enough, the composition of the present invention allows to obtain a short T_{max} of pravastatin, after administration of a fenofibrate-pravastatin combination with a standard meal (continental breakfast), see figure 1.

Different pharmaceutical formulations may be used to obtain this pharmacokinetic profile as the release of pravastatin is as rapid as possible and the release of fenofibrate occurs later. For instance, a capsule containing a coated or uncoated tablet of pravastatin with a semi-solid composition of fenofibrate is suitable.

Other alternatives are capsules containing pravastatin under the form of powder, pellets or tablets and fenofibrate formulated as paste, semi-solid tablet, granulated powder or pellets, coated or uncoated tablets.

To avoid simultaneous high plasma concentrations of both drugs, the combination may release pravastatin before and/or after fenofibrate. Also a slow pravastatin release during a period of time is acceptable. To release the pravastatin before the fenofibrate immediate release formulation shall be selected. The release of pravastatin after the release of fenofibrate can be achieved with delayed release formulation while the gradual release over a period of time can be achieved with a controlled or delayed and controlled release formulation.

Details and characteristics of composition of the invention are given in the attached claims. Advantageously the statin (preferably the pravastatin) is in a first solid or semi solid form which is free or substantially free of fibrate (especially fenofibrate), while the fibrate (preferably fenofibrate) is in a second solid or semi solid form which is free or substantially free of statin (especially pravastatin). Advantageously at least a coating layer forms a barrier between the first form and the second form.

Further details will also appear from the following description of examples, in which reference is made to the attached drawings.

Brief description of the drawings

Figure 1 represents the mean dissolution values (% of compound dissolved in function of the time expressed in minute) of six vessels for the pravastatin and the fenofibrate, while

Figure 2 gives the mean plasma concentration curves versus time for
5 fenofibric acid and pravastatin obtained after administration of the combination fenofibrate-pravastatin of example 4.

Examples

The invention is additionally illustrated in connection with the following
10 examples, which are considered to be illustrative of the present invention. It should be understood, however, that the invention is not limited to the specific details of the Examples.

Example 1

15

Ingredient Name	Amount [g]
Pravastatin Sodium Salt	20
Sodium bicarbonate	110
Ascorbyl palmitate	2
Lactose monohydrate	19
Cellulose microcrystalline	12
Povidone K30	2
Water for granulation	25
Magnesium stearate	2
Sodium starch glycolate	13

Lactose, sodium bicarbonate, ascorbyl palmitate, lactose monohydrate, cellulose microcrystalline and povidone K30 were blended in a planetary mixer for about 5 to 10 minutes until an homogeneous blend was obtained.
20 While under agitation, a solution containing the pravastatin sodium salt into the water for granulation was added to granulate the powders. The granules obtained were dried at about 40°C for about 5 hours. Thereafter

the dried granules were screened through a 1.0mm sieve, and further blended into a planetary mixer for about 2 minutes after the addition of the magnesium stearate and sodium starch glycolate.

The final mix was compressed into tablets using a rotary compressing machine equipped with punches of the deep cup type with a diameter of 6.5mm. The mean weight of the tablets was 180 mg. Corresponding to tablets containing 20 mg of pravastatin sodium salt. The tablet hardness was comprised between 4 and 6 kilopascals (Kp).

When the core tablet was placed into 100ml of demineralized water a pH of about 8.2 was measured.

Example 2

Ingredient Name	Amount [g]
Povidone K30	35
Talc	35
Triacetin	5
Absolute Alcohol	300

This coating solution was applied to the tablets from Example 1 using a pan coater. The amount of coating applied was about 14.4mg of dry coating (weight gain) per tablet.

Example 3

Ingredient Name	Amount [g]
Fenofibrate powder	160
Lauroyl macroglyceride (gelucire 44/14)	240
Polyethylene glycol 20,000	48
Hydroxypropylcellulose	95.0
Sodium starch glycolate	20.0
Ascorbyl palmitate	1.0

Gelucire 44/14 and polyethylene glycol 20,000 were added to a mixer equipped with a double wall bowl. The mixer was started and the bowl was warmed at about 75°C. When the gelucire and the polyethylene glycols were molten, the other ingredients (Fenofibrate, hydroxypropyl cellulose, sodium starch glycolate and ascorbyl palmitate) were added while maintaining the temperature at about 70 - 75°C.

Example 4

The combination product was obtained by filling, into size 0 elongated hard gelatin capsules, one tablet of Example 2 and 564mg of the hot blend of Example 3. After filling, the capsules were cooled by placing them on trays between 4 and 8°C.

The capsules obtained contained 20mg of pravastatin and 160mg of fenofibrate.

The capsules of Example 4 were submitted to a dissolution test using USP apparatus #2 at a speed of 100 rpm and 900 ml of an aqueous solution adjusted at pH5.5 with sodium hydroxide and containing 1.24g of potassium dihydrogen phosphate, 27g of polysorbate 80 and 2.88g of as dissolution medium. The pravastatin amounts dissolved after 10, 25, 35 and 45 minutes were measured by high performance liquid chromatography.

The fenofibrate amounts dissolved after 30, 60, 90, 120 and 180 minutes were measured by UV spectroscopy at a wavelength of about 281nm. Figure 1 represent the mean dissolution values of six vessels for the pravastatin and the fenofibrate.

This test shows very different in vitro releases profiles for pravastatin and fenofibrate. The pravastatin is almost completely dissolved after 45 minutes while it takes about 180 minutes for the fenofibrate to be completely dissolved.

To illustrate the present invention, a pharmacokinetic study has been performed in human healthy volunteers. The combination formulation of Example 4 consisting of a capsule containing 20 mg of pravastatin in a

coated tablet and 160mg of fenofibrate in a semi solid paste was administered to the six healthy volunteers following a standardized breakfast consisting of: Cold cuts, cheese, salad, bread, butter and jam or lasagna and 240ml of water.

- 5 The healthy volunteers were caucasians of both sexes aged from 18 to 50 years.

Blood samples were taken regularly up to 12 hours after administration. The drugs analysed were fenofibric acid and pravastatin. The concentrations obtained at each sampling point are shown in Table 2.

- 10 The mean plasma concentration curves versus time for fenofibric acid and pravastatin obtained after administration of the combination of example 4 are shown in Figure 2.

Table 2: Individual plasma levels of pravastatin [ng/ml] and fenofibric acid [μ g/ml] after administration of a capsule containing 160 mg of fenofibrate and 20 mg of pravastatin in 6 human volunteers. (Product of Example 4).

Pravastatin Plasma Levels [ng/mL]

samples	T0	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	T21	T22	AUCt	Cmax	Tmax
Hours	0,00	0,25	0,50	0,75	1,00	1,25	1,50	1,75	2,00	2,50	3,00	3,50	3,75	4,00	4,25	4,50	4,75	5,00	6,00	7,25	8,00	10,00	12,00	12,00		
sub 1	0,0	0,1	0,1	0,3	0,6	3,3	8,3	8,9	6,8	7,3	6,8	3,7	2,6	2,8	3,1	2,9	2,6	3,0	2,0	1,2	0,6	0,3	0,5	27,1	8,9	1,8
sub 2	0,0	0,0	0,0	0,0	0,1	0,0	0,1	0,4	1,4	4,7	4,4	3,3	2,9	1,4	1,4	0,9	1,0	1,1	0,4	0,5	0,1	0,0	0,0	10,2	4,7	2,5
sub 3	0,0	0,0	0,0	0,0	0,1	0,1	0,7	1,0	2,9	1,9	1,3	0,9	1,0	0,8	0,9	0,3	0,3	0,1	0,2	0,3	0,2	0,0	0,0	5,2	2,9	2,0
sub 4	0,0	0,0	1,5	16,7	25,9	25,3	24,6	26,4	24,0	18,1	10,5	14,5	10,9	3,8	4,1	3,3	3,0	2,7	2,0	1,9	1,1	1,1	0,4	74,9	26,4	1,8
sub 5	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,2	0,5	1,0	1,5	1,8	2,0	2,4	2,8	1,9	2,5	2,3	0,9	0,4	0,2	0,0	0,0	8,2	2,8	4,3
sub 6	0,0	0,4	0,6	5,2	11,3	21,9	20,6	22,7	16,4	8,7	7,3	5,4	4,2	4,1	4,4	2,7	3,0	2,9	2,3	2,0	1,8	0,8	0,4	52,3	22,7	1,8
Mean	0,0	0,2	0,7	7,4	12,6	16,9	18,1	19,8	17,3	13,9	10,6	9,9	7,9	5,1	5,6	4,0	4,2	4,0	2,6	2,1	1,3	0,7	0,4	59,3	22,8	2,3
SD	0,0	0,2	0,6	6,7	10,5	11,9	11,0	11,8	9,5	6,2	3,6	4,9	3,6	1,3	1,4	1,2	1,1	1,1	0,9	0,8	0,7	0,5	0,2	28,3	10,5	1,0

Fenofibrate Plasma Levels [μ g/ml]

samples	T0	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	T21	T22	AUCt	Cmax	Tmax
Hours	0,0	0,3	0,5	0,8	1,0	1,3	1,5	1,8	2,0	2,5	3,0	3,5	3,8	4,0	4,3	4,5	4,8	5,0	6,0	7,3	8,0	10,0	12,0			
sub 1	0,0	0,0	0,0	0,0	0,0	0,3	1,1	2,4	3,2	4,4	4,8	4,6	4,4	3,9	4,9	4,9	5,5	5,7	10,2	9,2	6,7	5,3	4,4	62,8	10,2	6,0
sub 2	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,2	1,1	2,1	3,2	3,9	6,3	6,6	8,0	7,3	8,8	10,3	6,8	10,9	8,2	7,5	73,8	10,9	8,0
sub 3	0,0	0,0	0,0	0,0	0,3	0,6	1,0	1,9	3,3	5,9	6,9	6,2	6,4	5,5	7,3	8,1	8,0	9,3	8,5	9,0	6,2	6,6	6,6	72,4	9,3	5,0
sub 4	0,0	0,0	0,0	0,5	1,7	2,9	3,6	4,5	4,8	5,8	7,0	8,3	9,3	8,5	8,7	8,0	7,4	6,9	6,8	5,2	5,2	4,1	3,5	60,9	9,3	3,8
sub 5	0,0	0,0	0,0	0,0	0,0	0,2	0,3	0,4	0,5	1,0	1,6	2,5	3,7	4,6	5,4	7,2	9,2	8,5	9,0	8,1	6,0	6,0	5,5	59,3	9,2	4,8
sub 6	0,0	0,0	0,0	0,0	1,0	3,9	7,4	10,9	10,9	11,8	10,9	10,4	9,7	9,4	9,1	8,9	8,5	7,6	7,4	6,2	5,1	4,1	3,4	74,5	11,8	2,5
Average	0,0	0,0	0,0	0,1	0,5	1,3	2,2	3,3	3,8	5,0	5,5	5,9	6,2	6,4	7,0	7,5	7,6	7,8	8,7	7,4	6,7	5,7	5,1	67,3	10,1	5,0
SD	0,0	0,0	0,0	0,2	0,7	1,7	2,8	4,0	3,9	4,0	3,5	3,1	2,7	2,2	1,7	1,4	1,2	1,3	1,4	1,6	2,2	1,6	1,7	7,0	1,1	1,9

It clearly appears that the invention allows indeed, to avoid simultaneous plasma peaks of both active ingredients, so allowing to minimize the risk of side effects due to the combination of drugs. Indeed, when the mean T_{\max} of fenofibric acid occurs (5 hours), the mean plasma concentration of pravastatin has already decreased to 4.0 ng/ml. Furthermore, the mean T_{\max} of fenofibric acid and of pravastatin are sufficiently separated. Indeed, the absolute difference of
|mean T_{\max} fenofibric acid – mean T_{\max} pravastatin| is equal to |5.0 – 2.3| or 2.7 hours.

10

Example 5

Ingredient Name	Amount [g]
Pravastatin Sodium Salt	40
Sodium bicarbonate	112
Lactose monohydrate	19
Cellulose microcrystalline	12
Povidone K30	2
Water for granulation	30
Magnesium stearate	2
Sodium starch glycolate	13

Lactose, sodium bicarbonate, lactose monohydrate, cellulose microcrystalline and povidone K30 were blended in a planetary mixer for about 5 to 10 minutes until an homogeneous blend was obtained. While under agitation, a suspension containing the pravastatin sodium salt into the water for granulation was added to granulate the powders. The granules obtained were dried at about 40°C for about 5 hours. After the dried granules were screened through a 1.0mm sieve, they were blend into a planetary mixer for about 2 minutes after the addition of the magnesium stearate and sodium starch glycolate. The final mix was compressed into tablets using a rotary compressing machine equipped with punches of the deep cup type with a diameter of 6.5mm. The mean weight of the tablets

was 200 mg. Corresponding to tablets containing 40 mg of pravastatin sodium salt. The tablets had hardness comprised between 4 and 6 kilopascals (Kp).

When a core tablet was placed into 100ml of demineralized water a pH of
5 about 8.3 was measured.

These core tablets were coated with the coating solution and the coating method parameters of Example 2.

Example 6

Ingredient	Amount [g]
Fenofibrate powder	160
Lactose	300
Povidone K30	15
Sodium Lauryl Sulfate	7
Crospovidone	15
Magnesium Stearate	3

10 Fenofibrate, lactose, povidone and sodium lauryl sulfate were blended in a planetary mixer and water was added to granulate. After oven drying for about 5 hours at 50°C, the granules were screened through a 1mm sieve. After addition of crospovidone and the magnesium stearate the granules that were blended for an additional 3 minutes in the planetary mixer.

Example 7

15 500 mg of lubricated granules of Example 6 and a tablet of Example 5 were filled into 0 elongated hydroxypropylmethylcellulose capsules to produce a combination product containing 40mg of pravastatin and 160mg of fenofibrate.

Example 8

Ingredient Name	Amount [g]
Pravastatin sodium salts	10
Sodium bicarbonate	40
Microcrystalline cellulose	100
Povidone K30	20
	<hr/>
	170

To the blend of all the ingredients in a planetary mixer was added water to
5 granulate. The paste obtained was extruded and spheronized in order to
obtain beads with a diameter of about 1mm. The beads were tray dried in
an oven at about 40°C for approximately 5 hours. The beads were
thereafter screened between 0.7mm and 1.4mm sieves.

Example 9

10 500 g of beads from Example 8 were coated with 200 g of coating solution
(which are equal to 40 g of dry residue) of Example 2 using a fluid bed
coater (Strea 1) equipped with a wurster column.

Example 10

A combination formulation was produced by filling 0 elongated hard gelatin
15 capsules with 500 mg of Fenofibrate lubricated granules of Example 6 and
170 mg of Pravastatin beads of Example 8.

The resulting combination formulation contained 10mg of pravastatin and
160mg of fenofibrate.

Example 11

20 Tablets of Pravastatin sodium salt with the composition as described in
Table1 were prepared following the method of Example 1 and thereafter
were coated with the insulation coating of Example 2.

From each of the tablets was produced a combination products by filling 0 elongated hard gelatin capsules with 564mg of the hot blend of Example 3 and a coated tablet as described in Table.

Each of these combination products were packaged in high density
5 polyethylene bottles with a desiccant.

The packaged product underwent a stability study under accelerated conditions at 40°C/75% relative humidity. The Pravastatin, Pravastatin Lactose and other impurities were measured by HPLC before and after 1 and 3 months of storage.

10 As a comparison the marketed tablets in Belgium Pravasine® 40 mg (Bristol Myers Squibb) have been stored in the same packaging. The Pravasine® 40 mg tablets correspond to the US patent 5,030,447 which claims to stabilize the pravastatin in a tablet form by using excipients able to produce a pH above 9 when the tablet is dissolved in water.

15

The results of stability are presented in the Table 3.

Table 1. Composition of Combination Product					
	Ingredient Amount [mg / tablet and capsule]				
Ingredient Name	11A	11B	11C	11D	11E
A. Pravastatin Tablet					
pravastatin Na	40	40	40	40	20
Na bicarbonate	112	110	80	/	/
Ca hydrogenophosphate	/	/	/	110	/
ascorbyl palmitate	/	2	/	/	/
Lactose	19	19	25	19	24
Microcrystalline cellulose	12	12	38	12	18.4
Polyvinylpyrrolidone	2	2	2	2	
sodium starch glycolate	13	13	13	13	14.4
magnesium stearate	2	2	2	2	3.2
mannitol	/	/	/	/	112
Insulation Coating	yes	yes	yes	yes	yes
pH of 1 tablet in 100mL of water	8.3	8.3	8.1	7.3	6.0
B. Fenofibrate					
Fenofibrate	160				
Gelucire 44/14	240				
PEG 20,000	48				
Hydroxypropylcellulose	95.0				
Sodium starch glycolate	20.0				
Lauryl palmitate	1.00				
0 elongated hard gelatin capsules	1 capsule				

Table 3: Stability of different batches of pravastatin tablets when combined with fenofibrate.

	After preparation	After 1 month	After 3 month
Example 11A			
Pravastatin	98.8	99.4	98.6
Pravastatin lactone	ND	ND	ND
other impurities	ND	0.07	0.12
Example 11B			
Pravastatin	98.9	100.7	100.8
Pravastatin lactone	ND	ND	ND
other impurities	0.05	0.05	0.10
Example 11C			
Pravastatin	99.5	98.8	97.7
Pravastatin lactone	ND	ND	0.20
other impurities	0.07	0.09	0.11
Example 11D			
Pravastatin	102.4	100.2	99.2
Pravastatin lactone	ND	0.34	1.18
other impurities	ND	0.07	0.28
Example 11E			
Pravastatin	98.0	NP	85.1
Pravastatin lactone	ND	NP	9.8
other impurities	0.12	NP	2.1
PRAVASINE 40 mg			
Pravastatin	103.7	103.2	103.5
Pravastatin lactone	ND	ND	0.11

other impurities	ND	0.22	0.25
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ND : Not detected

NP : Not performed

- 5 - the use of a alkaline agent conferring a pH less than 9 significantly improves the stability of pravastatin tablets since the batch containing no alkaline agent (Example 11E) has a lactone content of 9.8% after 3 months which is about 50 to 100 times more than the formulation containing such alkaline agent.
- 10 - the stability observed with the formulations of the present invention with tablets of pravastatin presenting a pH comprised between 7 to 9 presents stability properties which are at least as good, if not better, than the marketed product PRAVASINE®, which presents the inconvenient of having a pH, when dissolved in water, of about 10. As said before, these high pH values are
15 not very well compatible with the stomach environment.
- 20 - for pravastatin tablets containing sodium bicarbonate, it also appears that the amount of sodium bicarbonate per tablet is important since the tablets containing 112 mg of sodium bicarbonate (Example 11A) present slightly better stability results than the formulation containing 80 mg of sodium bicarbonate /
25 tablet (Example 11C).

25 The results of the present stability shows clearly that tablets prepared following the teachings of the present invention possesses very good stability characteristics while avoiding the need to use very alkaline substances as disclosed in US Patent 5,030,447 and 5,180,589.

Example 12

The example 12 is similar to example 1 where 1 g of folic acid has been added to the pravastatin component of the present combination formulation.

Ingredient Name	Amount [g]
Pravastatin Sodium Salt	20
Sodium bicarbonate	110
folic acid	1
Ascorbyl palmitate	2
Lactose monohydrate	19
Cellulose microcrystalline	12
Povidone K30	2
Water for granulation	25
Magnesium stearate	2
Sodium starch glycolate	13

Example 13

- 5 example 13 is similar to example 3 but where 3 mg of folic acid has been added to the fenofibrate component of the present combination formulation.

Ingredient Name	Amount [g]
Fenofibrate powder	160
Lauroyl macroglyceride (gelucire 44/14)	240
Polyethylene glycol 20,000	48
Hydroxypropylcellulose	95.0
folic acid	3.0
Sodium starch glycolate	20.0
Ascorbyl palmitate	1.0

CLAIMS

1. A controlled Release Pharmaceutical composition comprising an effective amount of Pravastatin and/or a pharmaceutical acceptable salt thereof and Fenofibrate said composition characterised that the difference, in absolute value, between the times of maximal concentration (T_{\max}) of Pravastatin and Fenofibric acid is not less than 1.5 hours upon administration with food to humans.
2. A composition following claim 1 wherein the difference, in absolute value, between the times of maximal concentration (T_{\max}) of Pravastatin and Fenofibric acid is not less than 1.5 hours when the composition is administered to human without food.
3. A composition according to claim 1 further containing a substance from the group of vitamins, minerals, nutrients and mixtures thereof.
4. A composition according to claim 3 where the vitamin derivative is folic acid, vitamin B6 or vitamin B12 or a mix of two or more of those vitamins
5. A composition according to claim 1 further containing between 0.05 and 100 mg of folic acid
6. A composition according to claim 1 containing an amount of Fenofibrate comprised between 5 and 300mg, advantageously between 25 mg and 300 mg.
7. A composition according to claim 1 containing an amount of Fenofibrate comprised between 5 mg and 200 mg, advantageously between 25 and 200mg.
8. A composition according to claim 1 containing an amount of Pravastatin and/or a pharmaceutical acceptable salt thereof comprised between 5 mg and 120 mg.

9. A composition according to claim 1 containing an amount of Pravastatin and/or a pharmaceutical acceptable salt thereof comprised between 10mg and 80mg.
- 5 10. An oral composition according to claim 1 characterized in that it is presented under the form of an hard gelatin, or hypromellose or any other pharmaceutically acceptable capsule.
11. A composition according to claim 1 characterised that the combination product is presented under the form of a tablet.
- 10 12. A composition according to claim 8 characterised that the Pravastatin into the capsule is present under the form of a tablet.
13. A composition according to claim 9 characterised in that the tablet containing the Pravastatin is coated with an hydrosoluble coating.
14. A composition according to claim 8 characterised that the Fenofibrate is present in the form of a semi-solid paste.
- 15 15. A composition according to claim 12 characterised in that the Fenofibrate is dissolved and/or dispersed into a polyglyceride.
16. A composition according to claim 8 characterised in that the Fenofibrate is present in a micronized form.
- 20 17. A composition according to claim 14 characterised in that the micronized Fenofibrate is coated onto an hydrosoluble carrier.
18. A composition according to claim 14 characterised in that the Fenofibrate is co-micronized with a surfactant.
19. A composition according to claim 14 characterised in that the Fenofibrate is blended and/or granulated with a surfactant.

20. A stable pharmaceutical composition comprising Pravastatin and/or a pharmaceutical acceptable salt thereof characterised in that it comprises an alkaline agent that will confer a pH of less than 9 when dissolved and/or dispersed in water.
- 5 21. A composition according to claim 20 characterised that the alkaline agent is selected from the group consisting of hydrogen carbonate or hydrogen phosphate metallic salts or any mixture thereof.
22. A composition according to claim 20 characterised that the alkaline agent used to stabilise the Pravastatin is selected from the group consisting of Sodium Bicarbonate, Sodium Hydrogen phosphate and mixtures thereof.
- 10 23. A composition according to claim 1 or 20 characterised in that it further comprises an antioxidant agent
24. A composition according to claim 23 wherein the antioxidant is selected from the ascorbic acid, ascorbic acid derivatives, vitamin E, vitamin E derivatives, propylgallate, butylhydroxyanisole, butylhydroxytoluene, sulfite.
- 15 25. A composition according to claim 24 wherein the antioxidant is ascorbyl palmitate.
- 20 26. The composition of claim 1 characterised in that it is suitable for once a day administration to humans.
27. A composition according to claim 24 characterized in that it may be administered in the morning or in the evening.
28. The composition of claim 1 useful for the treatment of hypercholesterolemia and/or hyperlipidemia.
- 25

29. A method of treatment of hypercholesterolemia and/or hyperlipidemia which comprises a once daily oral administration of the composition of claim 1.

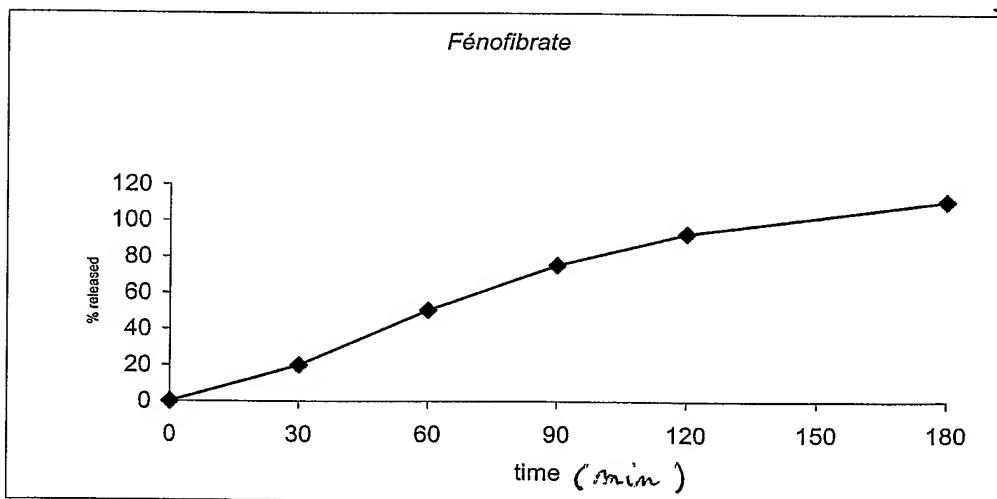
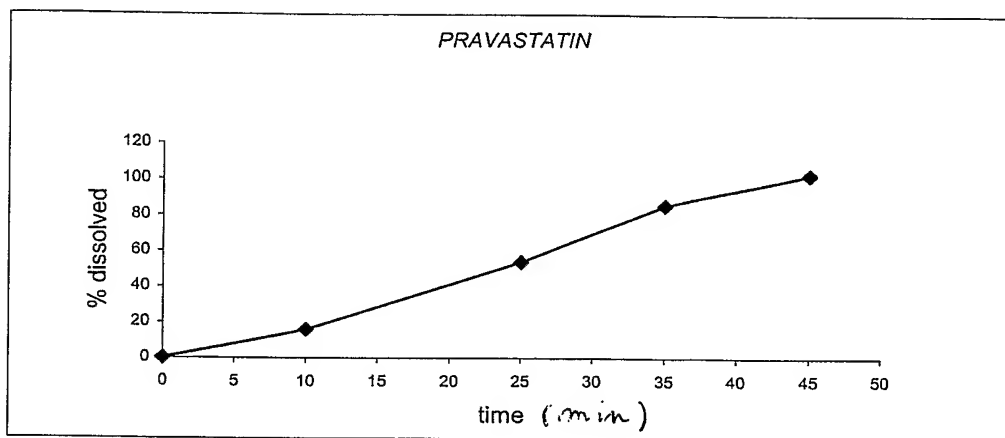
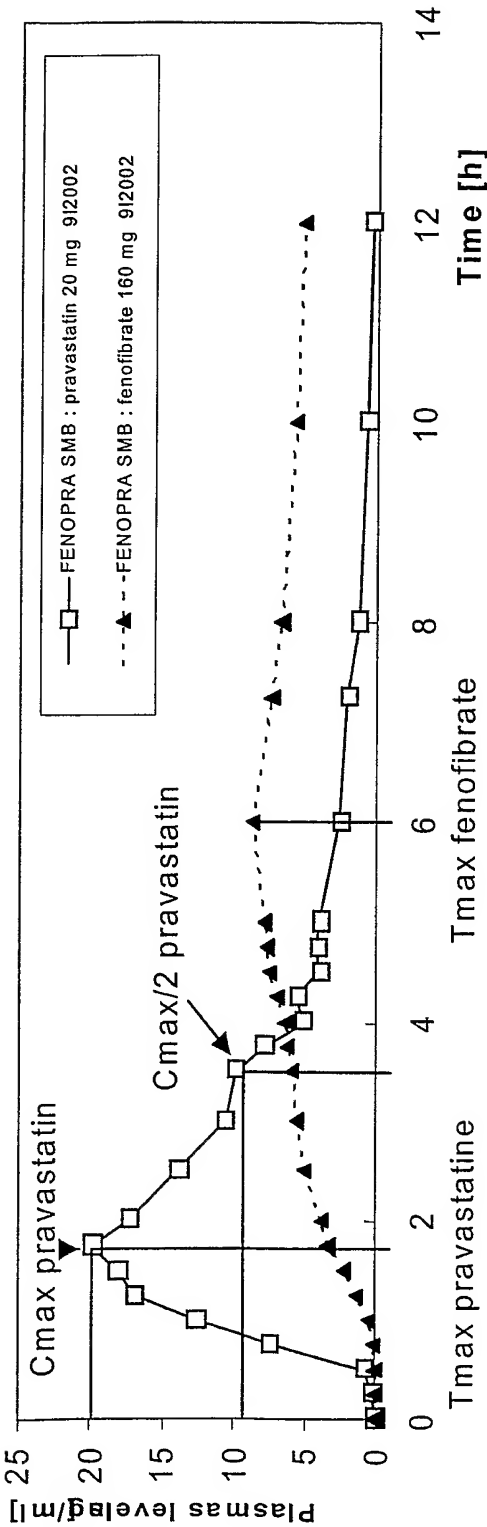
Fig. 1

Fig. 2



INTERNATIONAL SEARCH REPORT

International Application No

PCT/BE 03/00133

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/36 A61K9/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/161032 A1 (GUIVARC H POL-HENRI W ET AL) 31 October 2002 (2002-10-31) cited in the application paragraph [0019] - paragraph [0020] paragraph [0071] paragraph [0082] paragraph [0135] paragraph [0240] - paragraph [0241] claims 1,15,35,45	1,2, 6-10, 16-18, 26-29
X	WO 03/013608 A (GALEPHAR M F ; SERENO ANTONIO (BE); BAUDIER PHILIPPE (BE); VANDERBIST) 20 February 2003 (2003-02-20) page 4, line 29 - page 7, line 2	1-3, 6-15,19, 23,24, 26-29
Y	examples 3,4	1-7, 14-16,18

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

19 July 2004

Date of mailing of the international search report

- 5 NOV 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

VON EGCELKRAUT, S

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/013501 A (SERENO ANTONIO ; SMB SA LAB (BE); BAUDIER PHILIPPE (BE); VANDERBIST FR) 20 February 2003 (2003-02-20) page 5, line 13 - line 26 examples	1,2,6,7, 14,15
Y	US 2003/049314 A1 (LIANG MATTHEW H ET AL) 13 March 2003 (2003-03-13) paragraph [0001] paragraph [0050] paragraph [0092] - paragraph [0102] examples 1,2	3-5
Y	US 6 368 620 B2 (LIU RONG ET AL) 9 April 2002 (2002-04-09) column 2, line 38 - line 54 example 3	16,18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/BE 03/00133

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 29 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-19 (completely); 23-25,27 (partially)

Controlled release pharmaceutical composition comprising pravastatin and fenofibrate, said composition being characterised that the difference between in times of maximal concentration (Tmax) of pravastatin and fenofibric acid is not less than 1.5 hours upon administration with food to humans.

2. claims: 20-22 (completely); 23-25,27 (partially)

Stable pharmaceutical composition comprising pravastatin characterized in that it comprises an alkaline agent that will confer a pH of less than 9 when dissolved and / or dispersed in water.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 29 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern Application No

PCT/BE 03/00133

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2002161032	A1	31-10-2002	US 2004086571 A1	06-05-2004
			AU 6294501 A	02-04-2002
			CA 2423335 A1	28-03-2002
			CA 2440355 A1	06-09-2002
			EP 1361867 A1	19-11-2003
			EP 1322289 A1	02-07-2003
			JP 2004523552 T	05-08-2004
			WO 0224169 A1	28-03-2002
			WO 02067901 A1	06-09-2002
			US 2002056206 A1	16-05-2002
WO 03013608	A	20-02-2003	WO 03013607 A1	20-02-2003
			WO 03013501 A1	20-02-2003
			WO 03013500 A1	20-02-2003
			WO 03013608 A1	20-02-2003
			CA 2456713 A1	20-02-2003
			CA 2456732 A1	20-02-2003
			EP 1414433 A1	06-05-2004
			EP 1414496 A1	06-05-2004
WO 03013501	A	20-02-2003	WO 03013607 A1	20-02-2003
			WO 03013501 A1	20-02-2003
			WO 03013500 A1	20-02-2003
			WO 03013608 A1	20-02-2003
			CA 2456713 A1	20-02-2003
			CA 2456732 A1	20-02-2003
			EP 1414433 A1	06-05-2004
			EP 1414496 A1	06-05-2004
US 2003049314	A1	13-03-2003	NONE	
US 6368620	B2	12-07-2001	US 2001007669 A1	12-07-2001